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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/812,642	03/30/2004	Nikos Pagratis	NEX87/C2	5220

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EXAMINER	
VIVLEMORE, TRACY ANN	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 02/28/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/812,642	PAGRATIS ET AL.	
	Examiner	Art Unit	
	Tracy Vivlemore	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 November 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-18* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *30 March 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *see box 6*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *See Continuation Sheet*.

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of SEQ ID NO: 115 in the reply filed on November 30, 2005 is acknowledged. The traversal is on the ground(s) that previous applications have been examined without a requirement of election of a single nucleotide sequence and that in previous applications no nucleic acid ligands searched were found in public databases. The documents submitted in support of this argument have been reviewed but the arguments presented are not found persuasive because although previous examiners did not require restriction between nucleotide sequences, current Office practice necessitates such an election.

The requirement is still deemed proper and is therefore made FINAL.

Claim Objections

Claims 2, 8 and 14 are objected to because of the following informalities: each of these claims contains non-elected subject matter, specifically the non-elected sequences. Additionally, each of these claims recites, "...the nucleic acid ligand of TGFβ2 is a ligand comprising a ligand having a nucleotide sequence...", which is redundant. It is suggested that this claim recite, "...the nucleic acid ligand of TGFβ2 comprises a ligand having a nucleotide sequence...".

Claim 13 is objected to because of the following informalities: the claim is non-grammatical. It is directed to a method of treating "a TGFβ2-mediated pathological conditions". Appropriate correction is required.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and In *re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to

be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-18 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 9-14 of U.S. Patent No. 6,713,616 and claims 2-4 of U.S. Patent No. 6,346,611. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims are directed to methods of using the compounds claimed in each of the patents. The '616 and '611 patents are directed to compounds comprising TGFβ2 nucleic acid ligands that may be conjugated to PEG, including the specific compound comprising SEQ ID NO: 115. The claims of the patents are directed to TGFβ2 nucleic acid ligands including the specific compound of SEQ ID NO: 115. Although the patented claims are directed to compounds, their patentability is considered in view of the ability to make and use the compound. The uses of these compounds recited in the instant claims are considered to be obvious in view of the patentability of the compounds.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the

art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-18 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

Claims 1-6 are directed to methods of inhibiting a TGFβ2 by contacting the TGFβ2 with a nucleic acid ligand of TGFβ2. Claims 7-12 are directed to methods of targeting a nucleic acid ligand to a site in a patient comprising TGFβ2 by covalently linking the nucleic acid ligand to either a non-immunogenic, high molecular weight compound or a lipophilic compound and administering the complex to a patient comprising TGFβ2. Claims 13-18 are directed to methods of treating a TGFβ2-mediated pathological condition by administering a nucleic acid ligand capable of binding to TGFβ2 to a patient in need thereof.

Claims 1-6 encompass the use of a nucleic acid ligand for inhibition of "a TGFβ". The genus of compounds that are capable of inhibition of TGFβ from any species is very large. The specification describes the structure of numerous nucleic acid ligands targeted to human TGFβ2 and assays to test the efficacy of these ligands in reversing TGFβ2-mediated inhibition of cell proliferation. The specification does not describe the full genus of nucleic acid ligands to human TGFβ2 by describing the structural features shared by the disclosed nucleic acid ligands that provide the function of inhibiting

human TGFβ2 and does not disclose the structure of any nucleic acid ligands that function to inhibit TGFβ2 from any species other than human.

Claims 7-12 are directed to a method of targeting a nucleic acid ligand to a site in a patient comprising TGFβ2. Although the patient comprises TGFβ2, the method encompasses the targeting of nucleic acid ligands that are not directed to TGFβ2 to any site within the patient. Additionally, the method is directed to targeting nucleic acid ligands to a patient of any species that comprises TGFβ2. The claim recites conjugation of a nucleic acid ligand with a non-immunogenic high molecular weight compound or a lipophilic compound as necessary for targeting the nucleic acid ligand to a site within a patient. The specification does not describe a representative sample of sites within a patient that can be targeted by administration of such conjugates.

Claims 13-18 encompass the treatment of any TGFβ2-mediated pathological disorder in any species. The prior art teaches that biological activities of TGFβ include immunosuppression and both inhibition and stimulation of cell proliferation, TGFβ is associated with cancer cell growth and metastasis and possibly is associated with autoimmune and infectious disease. The prior art further teaches that antisense oligonucleotides have been reported to prevent glioma formation in rats. Neither the specification nor the prior art describes the full genus of pathological disorders that are mediated by TGFβ2, particularly in view of the teachings that TGFβ2 can both increase and decrease cellular proliferation and that TGFβ2 may be involved in autoimmune disorders and infectious diseases. Nor does the specification describe the structure of

any nucleic acid ligands that have the function of treating any TGFβ2-mediated pathological conditions in any species.

Claims 1-18 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for use of a nucleic acid ligand to TGFβ2 to inhibit TGFβ2-mediated proliferation of cultured cells, does not reasonably provide enablement for targeting a nucleic acid to a site in a patient, inhibition of TGFβ2 *in vivo* or treatment a pathological condition mediated by TGFβ2 *in vivo* in any organism using a nucleic acid ligand to TGFβ2. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The following factors as enumerated *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), are considered when making a determination that a disclosure is not enabling: the breadth of the claims, the nature of the invention, the state of the prior art, the level of ordinary skill in the art, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples and the quantity of experimentation needed to make the invention based on the content of the disclosure.

Claims 1-6 are directed to methods of inhibiting a TGFβ2 by contacting the TGFβ2 with a nucleic acid ligand of TGFβ2. Claims 7-12 are directed to methods of targeting a nucleic acid ligand to a site in a patient comprising TGFβ2 by covalently linking the nucleic acid ligand to either a non-immunogenic, high molecular weight

compound or a lipophilic compound and administering the complex to a patient comprising TGFβ2. Claims 13-18 are directed to methods of treating a TGFβ2-mediated pathological condition by administering a nucleic acid ligand capable of binding to TGFβ2 to a patient in need thereof. The claims are directed to both *in vitro* embodiments and *in vivo* embodiments where a TGFβ2 nucleic acid ligand is administered to target a site within a patient or treat a TGFβ2-mediated disorder.

The specification teaches the isolation of nucleic acid ligands targeted to human TGFβ2 and assays to test the efficacy of these ligands in reversing TGFβ2-mediated inhibition of cell proliferation. The prior art teaches that biological activities of TGFβ include immunosuppression and both inhibition and stimulation of cell proliferation, TGFβ is associated with cancer cell growth and metastasis and possibly is associated with autoimmune and infectious disease. The specification describes the administration of nucleic acid ligands to rats for determination of plasma half-life, residence time and clearance rate. The specification does not provide any examples of using TGFβ2 nucleic acid ligands for the purpose of treating any TGFβ2-mediated pathological conditions in any species.

Problems related to *in vivo* and therapeutic use of nucleic acids were well known in the art at the time of invention (see for example Opalinska et al. (Nature Reviews Drug Discovery, 2002, vol. 1, p. 503-514)). Such problems include the inability to specifically deliver an effective concentration of a nucleic acid to a target cell, such that a target gene is inhibited to a degree necessary to result in a significant or therapeutic effect.

Opalinska et al. state on page 511

"[I]t is widely appreciated that the ability of nucleic-acid molecules to modify gene expression *in vivo* is quite variable, and therefore wanting in terms of reliability. Several issues have been implicated as a root cause of this problem, including molecule delivery to targeted cells and specific compartments within cells and identification of sequence that is accessible to hybridization in the genomic DNA or RNA" and in column 2 of the same page, "Another problem in this field is the limited ability to deliver nucleic acids into cells and have them reach their target. Without this ability, it is clear that even an appropriately targeted sequence is not likely to be efficient. As a general rule, oligonucleotides are taken up primarily through a combination of adsorptive and fluid-phase endocytosis. After internalization, confocal and electron microscopy studies have indicated that the bulk of the oligonucleotides enter the endosome-lysosome compartment, in which most of the material becomes either trapped or degraded."

Given this unpredictability, the skilled artisan would require specific guidance to practice the claimed methods *in vivo* in all organisms, with a resultant inhibition of gene expression, as claimed. The specification provides examples of the use of nucleic acid ligands to TGFβ2 to prevent TGFβ2-induced inhibition of proliferation in mink lung epithelial cells, however, cell culture examples are generally not predictive of *in vivo* inhibition and the methods of delivery of the exemplified cell line would not be applicable to delivery of oligonucleotides to any organism. Due to differences in the physiological conditions of a cell *in vitro* versus *in vivo*, the uptake and biological activity observed *in vitro* would not predictably translate to *in vivo* results. Given these teachings, the skilled artisan would not know *a priori* whether introduction of oligonucleotides *in vivo* by the broadly disclosed methodologies of the instant invention would result in the oligonucleotide reaching the proper cell in a sufficient concentration and remaining for a sufficient time to provide successful inhibition of expression of a target gene. In fact, the state of the art is such that successful delivery of oligonucleotide sequences *in vivo* or *in vitro*, such that the polynucleotide or oligonucleotide provides the requisite biological effect to the target cells/tissues/organs, must be determined empirically.

The specification does not provide the guidance required to overcome the art-recognized unpredictability of using nucleic acids in therapeutic applications in any organism. The teachings of the prior art do not provide that guidance, such that the skilled artisan would be able to practice the claimed *in vivo* and therapeutic methods. The amount of experimentation required is such that one of skill in the art could not practice the invention commensurate in scope with the claims without undue, trial and error experimentation and therefore, claims 1-18 are not enabled.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Tracy Vivlemore whose telephone number is 571-272-2914. The examiner can normally be reached on Mon-Fri 8:45-5:15.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on 571-272-0811. The central FAX Number is 571-273-8300.

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For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Tracy Vivlemore
Examiner
Art Unit 1635

TV
February 9, 2006

J.D. SCHULTZ, PH.D.
PATENT EXAMINER

Continuation of Attachment(s) 6). Other: IDS of 6/17/04,6/25/04,6/29/04,1/05 and 9/05.